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Office of Vaccines Research and Review,
Center for Biologics Evaluation and Research
FDA

Combination Vaccines Containing *Haemophilus influenzae* type b (Hib): Immune Correlates of Protection Against Invasive Hib Disease and Potential Clinical Significance of Reduced Anti-PRP Polysaccharide Responses

Introduction

The development of combination vaccines has received increased emphasis, in part due to the increasing number of recommended childhood vaccines and thus the number of injections required (Guess 1999). Combination vaccines are defined as providing protection against two or more diseases or against multiple serotypes of a single disease (CBER 1997). Although numerous combinations are possible, vaccines that combine *Haemophilus influenzae* type b conjugate (Hib) and diphtheria toxoid, tetanus toxoid and acellular pertussis (DTaP) are attractive for development because they combine components, often already licensed as separate vaccines, that are required in the recommended childhood immunization schedule. However, development and licensure of DTaP-Hib combination vaccines has been hampered by immune interference in the polyribosylribitol phosphate (PRP) polysaccharide antibody responses observed in some DTaP-Hib combinations, when compared with separate injection of the DTaP and Hib component vaccines. Clinical development of various combinations has been pursued to decrease the number of injections *and* avoid potential immune interference observed in the DTaP-Hib combinations, including Hib-Hepatitis B (HepB) vaccine, DTaP-HepB-IPV, and others.

This session has been organized to openly discuss and elicit expert opinion regarding the scientific and regulatory challenges associated with developing combination vaccines containing Hib conjugates.

Background

The regulation of new combination vaccines poses particular challenges. In reviewing combination vaccines, the FDA is required to follow the Code of Federal Regulations (CFR); two specific citations are directly applicable. As per 21 CFR 300.50, a fixed combination prescription drug must demonstrate that each component makes a contribution to the claimed treatment effects, and that the dosage is such that it is **safe** and **effective** (Code of Federal Regulations 1997). In addition, 21 CFR 601.25(d)(4) states that safe and effective active components may be combined if each component makes a contribution to the claimed effects, **combining does not decrease purity, potency, safety or effectiveness of the individual components** [emphasis added], and when used correctly, provides preventive therapy or treatment (Code of Federal Regulations 1997). In 1997, the FDA issued a "Guidance for industry for the evaluation of combination vaccines for preventable diseases: Product, testing and clinical studies" to assist industry in the manufacture and testing of combination vaccines

(CBER 1997). This document provides guidance on how the regulations might be implemented in the testing of combination products.

Demonstration of efficacy is required for licensure of vaccines; however, placebo-controlled clinical endpoint efficacy trials may be unethical once a vaccine for a particular antigen is licensed in that country. Active, comparative controlled studies would be acceptable to the FDA, but would necessitate very large sample sizes. If, by scientific consensus, serologic correlate(s) of protection have been established for a particular antigen, the FDA has generally accepted pivotal immunogenicity studies in lieu of field efficacy trials. Following efficacy trials of Hib polysaccharide vaccines (not Hib-conjugates) in the late 1970s-early 1980s, correlates of protection were proposed which have been generally accepted (Peltola et al. 1977; Kayhty et al. 1983). Based on these studies and data from passive antibody studies, a post-vaccination antibody level of 0.15 µg/ml was accepted as correlating with at least short-term protection (Robbins et al. 1973) and 1.0 µg/ml as correlating with long-term protection (Kayhty et al. 1983; Anderson 1984).

Although efficacy trials with clinical endpoints have demonstrated the effectiveness of several Hib conjugate vaccines (Black et al. 1991; PedvaxHIB® package insert; Heath et al. 1998), serology has also been used to evaluate the effectiveness of Hib conjugate vaccines (ActHIB® package insert) and combination vaccines containing Hib components (ActHIB® package insert, TETRAMUNE® package insert). In the latter case, the geometric mean concentration of anti-PRP response, as well as the percentage of children achieving both 0.15 µg/ml and 1.0 µg/ml of anti-PRP antibody concentrations were assessed. However, the relevance of these levels with respect to Hib conjugate products has been questioned. When evaluating combination vaccines, CBER's guidance for industry on combination vaccines recommends that clinical trials compare the immune responses elicited by the combination vaccine versus separate injections, and that these trials be conducted to demonstrate non-inferiority of the combination vaccine (CBER 1997).

VRBPAC Agenda

This VRBPAC session will include presentations and discussion on the following (see attached agenda):

- Historical perspective and current understanding of the immunologic correlates of protection against invasive Hib disease
- Data from two studies evaluating a combination DTaP-Hib-conjugate vaccine
- Potential clinical significance of reduced anti-PRP polysaccharide response
  - Field experience with Hib vaccines in a high-risk population (Alaskan natives)
  - Hib antibodies and field efficacy of Hib conjugate vaccines in Germany and the United Kingdom
  - Immunological basis for reduced anti-PRP responses in combination vaccines containing Hib conjugates
- Trial design and statistical analysis of the immune response in combination vaccines

Prior Experience with Combination Vaccines Containing Hib and DTwP

Currently, two whole cell pertussis-containing vaccines (DTwP)-Hib conjugate combinations are licensed for use in infants. TETRAMUNE® is a combination product formulated as DTP-(PRP-HbOC) which was shown to induce equal or better immune responses to all vaccine antigens compared to the responses induced by the separate injections (TETRAMUNE® package insert). The second combination product is DTP used to reconstitute ActHIB® (PRP-T). When admixed, this combination product was shown to induce anti-PRP concentrations of $\geq$1.0 µg/ml in 85-90% of the children post-dose 3 (ActHIB® package insert).

Given the ACIP's expressed preference for acellular pertussis-containing vaccines (DTaP) in the childhood immunization schedule, and the similar schedules for Hib and DTaP vaccines, there has been increased interest in the development of combination vaccines containing these components. Summarized below, and illustrated in Tables 1 and 2, are serologic data for combination products containing Hib conjugates currently under development for use in infants.

Data on Combination Vaccines Containing Hib Conjugates and DTaP

TriHIBit® for infant indication

One approach taken for combination vaccine development has been to utilize currently licensed individual components. For example, TriHIBit® (*Haemophilus influenzae* type b Conjugate Vaccine reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is composed of Tripedia® (DTaP) and ActHIB® (PRP-T) which are admixed immediately prior to administration. TriHIBit® was approved for use in children 15-18 months of age based on clinical studies which showed that 100% of the children who received TriHIBit® achieved an anti-PRP antibody concentration of $\geq$1.0 µg/ml (ActHIB® package insert). Clinical development plans for this product included the proposed use in children at 2, 4 and 6 months of age. The data obtained following administration of TriHIBit® at 2, 4, and 6 months of age are summarized as follows:

Two studies, intended to support licensure of TriHIBit® for the infant indication, evaluated the immune response of TriHIBit® administered concomitantly with OPV at 2, 4, and 6 months of age (Table 1). (Note: These studies were conducted when OPV was the preferred poliovirus vaccine regimen.)

Study 468-01 showed that at 7 months of age, 100% of the subjects who received the separate injections achieved anti-PRP concentrations of $\geq$1.0 µg/ml, compared to 85% of the infants who received TriHIBit®. Of note, the point estimate for the difference between the combination vaccine minus separate administration groups (C-S) was -14.7%, with the lower bound of the 95% confidence interval (CI) for the difference being -22.7%.

Study 468-08 showed a lower anti-PRP response relative to study 468-01 for both separate and combined groups, with 78% and 74% of the children, respectively, achieving an anti-PRP concentration of ≥1.0 µg/ml post-dose 3. Of note, the point estimate for the difference (C-S) in the responses between the groups was -3.4%, with the lower bound of the 95% CI for the difference being -16.3%. These data were presented before the VRBPAC in June 1997. Based on concern expressed by the committee members over the diminished anti-PRP response seen in study 468-01 and the lack of statistical power for study 468-08, additional data were sought from two studies already underway.

The original objective of these two additional studies was to evaluate the immune responses for TriHIBit® when administered with OPV, IPV and the sequential IPV/OPV schedule.

- Data generated under NIAID's IND 6782 (principal investigator: Dr. Margaret Rennels) evaluated immunologic responses following concurrent administration of TriHIBit® with either OPV, IPV, or a sequential schedule, compared with separate injections of DTaP and PRP-T given concurrently with OPV (Table 1) (Rennels 1998). Unexpectedly, a significant decrease in anti-PRP concentrations was observed in children receiving 2 or 3 doses of IPV concurrently with TriHIBit® compared to those given OPV concurrently with either TriHIBit® or DTaP and PRP-T as separate injections.

The percentage of children achieving an anti-PRP concentration of **≥0.15** µg/ml in the TriHIBit® and IPV group was 85%, (lower bound of the 95% CI being 78%). In addition, the percentage of children achieving an anti-PRP response ≥1.0 µg/ml was also significantly reduced when TriHIBit® was administered concomitantly with 3 doses of IPV. In this group, only 53% (lower bound of the 95% CI being 44%) of the children achieved an anti-PRP concentration of ≥1.0 µg/ml. When compared to the response obtained in the control group (separate administration of DTaP, PRP-T, OPV), there was a -29% difference (C-S, lower bound of the 95% CI being -40%) in the percentage of children achieving ≥1.0 µg/ml for the group administered TriHIBit® concomitantly with IPV.

- Data generated under IND 6905 (conducted by Dr. Robert Daum) evaluated anti-PRP responses when TriHIBit® was administered concomitantly with OPV or IPV at two separate clinical sites. In contrast to the study conducted under IND 6782, this study did not have a separate injection control group of DTaP and PRP-T. Of note, when data from the two clinical study sites were compared, differences in Hib immune responses were observed (Table 2) (unpublished data). At the Chicago site, 100% of the subjects who received TriHIBit® concurrently with OPV achieved anti-PRP concentrations of **≥0.15** µg/ml compared to 90% of subjects achieving this same level at the New Orleans site. A similar site difference was observed when TriHIBit® was administered concomitantly with IPV in that 95% of the subjects at the Chicago site achieved anti-PRP concentrations of ≥0.15 µg/ml compared to 82% at the New Orleans site. The differences between clinical study sites were more pronounced when the percentage of children achieving ≥1.0 µg/ml anti-PRP concentrations was evaluated. The percentage of children achieving ≥1.0 µg/ml when TriHIBit® was administered with IPV was 81% and 62% for the Chicago and New Orleans sites, respectively. Confidence intervals for the various point estimates are not yet available.

Other Combination Products Containing Hib Conjugates Demonstrating Interference

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Combination Products Containing Hib Conjugates that Demonstrate Minimal Interference

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Alternative Combination Vaccines for the Infant Schedule

The development of combination vaccines has not been limited to the combination of DTaP and Hib conjugates. As mentioned earlier, one strategy for combination product development is to combine two licensed vaccines into a single formulation. For example, COMVAX® (Hepatitis b and PRP-OMP combination vaccine) has been licensed for use in children. Studies of COMVAX® compared to separate injections of PedvaxHIB® and RECOMBIVAX HB® showed no suggestion of immunologic interference of the anti-PRP response, i.e., 72% versus 76% achieving $\geq$1.0 µg/ml anti-PRP concentration post-dose 2, respectively (COMVAX® package insert).

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Regulatory Issues

Recent clinical experience with combination vaccines containing Hib conjugates and DTaP pose special regulatory concerns for CBER:

1. Given the regulatory requirement that combination products show "no decrease in safety, potency and effectiveness of the combination product" relative to the separate components, how should CBER view diminished Hib immune responses observed with certain combination vaccines when compared to separately injected components?

2. Does an individual's protection against invasive Hib disease require a critical circulating antibody level, prior to induction of an anamnestic response?

3. What is the clinical relevance of reduced Hib responses observed with some combination vaccines if such vaccines were to be licensed?

a. Would infants and young children, particularly those in high-risk populations (such as Native Americans and Alaskan natives) be at increased risk of developing invasive Hib disease upon encounter with the organism?

b. If there were an increased risk, how should the risk of additional cases of invasive Hib disease in the U.S. be balanced against the advantages of new combination products containing Hib conjugates?

Proposed Approaches

Several approaches have been proposed by manufacturers and investigators in an effort to address these questions:

1. Demonstration of "priming". Some investigators and sponsors have proposed that the lowered immune response seen with certain combination vaccines containing Hib is not clinically relevant because such infants are "primed" should they be challenged with the organism (Zepp et al. 1997; Pichichero et al. 1999). Evaluation of the immune response to unconjugated PRP polysaccharide as a booster dose has been suggested to demonstrate adequate priming (Zepp et al. 1997; Hoppenbrouwers et al. 1999). In several studies, investigators have observed large spontaneous increases in Hib polysaccharide antibody in children followed long-term after conjugate immunization, which they attributed to natural boosting.

When evaluating studies designed to demonstrate that children were adequately primed by the primary series, CBER must ascertain the significance of the qualitative and quantitative antibody levels obtained. In addition, CBER must determine whether the kinetics associated with the unconjugated PRP booster mimic that observed following natural infection or that observed with licensed products that were shown to be efficacious in vaccine field trials.

Several reports have suggested that demonstration of an anamnestic response (Zepp et al. 1997; Hoppenbrouwers et al. 1999) and changes in antibody avidity are possible measures of immunologic memory (Goldblatt et al. 1998; Granoff and Lucas 1995; Pichichero et al., 1999). For example, in the Finnish efficacy study for PRP-D, anamnestic booster responses in children with low responses to the primary immunization were viewed by the authors to be evidence of priming (Eskola et al. 1999; Kayhty et al. 1993; Decker et al. 1993). This vaccine, PRP-D, had a high level of efficacy in a Finnish Efficacy trial when used to immunize children at 3, 4, 6 and 14-16 months of age (Eskola et al. 1990). However, this same vaccine was not efficacious among Alaskan native infants immunized at 2, 4, and 6 months of age (Ward et al. 1990). Explanations proposed for this variation in efficacy include differences in the epidemiology of invasive Hib disease (e.g., higher Hib carriage and younger age distribution of disease in Alaskan infants) and related socioeconomic factors (e.g., crowding) leading to an increased chance of infection (Eskola and Kayhty 1994). Given the different efficacy outcomes observed in Finnish versus Alaskan infants for PRP-D conjugate vaccine, the correlation between priming and the protective efficacy for vaccines with reduced anti-PRP responses remains uncertain.

2. Comparison with historical experience or other licensed Hib conjugate vaccines. A second proposed approach is to evaluate the response to the combination product without

requiring simultaneous comparison to a separate injections control group. Using this approach, the anti-PRP immune response to combination products would be compared with responses to the individual components, using historical experience across multiple studies and over time. Similarly, some investigators have proposed comparing the immune response of combination products to that observed with different licensed Hib conjugate vaccines, again using historical experience across multiple studies and over time.

However, there are several weaknesses to the approach of using historical comparisons in evaluating combination products containing Hib conjugate vaccines. First, inherent differences across studies, including population demographics, immunization schedules, concurrent vaccinations, serologic assays, changes in vaccine formulation, etc. make a comparison of data across different studies difficult to interpret. In addition, even a direct, randomized comparison of anti-PRP responses between Hib conjugate vaccines with different carrier proteins has limitations because of qualitative differences in the anti-PRP responses, i.e., effects of different carrier proteins on efficacy, avidity, and isotype induction. This concern is based on data obtained in laboratory analyses (Granoff and Lucas 1995), as well as by field experience (Eskola et al. 1999; Eskola et al. 1990; Ward et al. 1990).

3. Use of post-licensure studies. Lastly, post-marketing evaluations, in the form of observational or controlled studies, or epidemiologic surveillance programs have been proposed to assess the effectiveness of combination vaccines containing Hib conjugates with variable immune responses. Data are available on post-licensure evaluations of Hib vaccines (Ward et al. 1990; Eskola and Kayhty 1994; Schmitt et al. 1999; Bisgard et al. 1998) and some manufacturers have proposed that such evaluations provide post-licensure assurance of combination vaccine effectiveness. However, post-licensure studies may be observational in nature, often lack a control arm, often are not randomized, and rarely, if ever, evaluate efficacy. Moreover, data from these studies typically are not available until 2 or more years post-licensure.

Alternatively, national epidemiologic surveillance systems or programs for active laboratory-based surveillance of diseases have been proposed to monitor vaccine effectiveness. However, national epidemiologic data on invasive Hib disease may not be a complete representation of disease burden due to underreporting of cases (Wenger 1998). In addition, specific data on Hib conjugate vaccines might be lacking because of incomplete ascertainment by investigators, and underreporting (i.e., did not provide known data) by investigators to the CDC. Therefore, each reported *H. influenzae* case in a child < 5 years of age is followed-up to ascertain serotype; and for Hib cases, to ascertain a complete vaccination history. A similar protocol is followed by the CDC's active laboratory-based surveillance system. In 1999, the population under surveillance totaled 26 million persons (Personal communication from Dr. Nancy Rosenstein, CDC).

By follow-up of each reported Hib case, a trend may be seen of Hib invasive disease cases by vaccine type administered. Follow-up of a reported increase in invasive Hib cases in Alaska in 1996 documented the lack of protection of one Hib vaccine in this high-risk population (Galil et al. 1999). However, to estimate vaccine effectiveness by vaccine type with this screening method knowledge of market share, doses administered, and estimated coverage levels is required. Analytic studies, such as population-based case-control studies using reported cases from the active, laboratory-based surveillance system, have been performed in the recent past but

these studies are both labor- and time-intensive (Jafari et al. 1999). Additionally, significant lag time may exist before a particular vaccine obtains widespread use and develops a cohort in which effectiveness can be assessed. Thus, post-marketing evaluations may not provide timely information on the effectiveness of combination vaccines containing Hib conjugates which demonstrated lower immune responses when compared to currently licensed vaccines.

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DRAFT Discussion points for VRBPAC (subject to change prior to meeting)

1. **Please discuss the appropriateness of the immunologic correlates of protection that the FDA is currently using to assess the efficacy of Hib vaccines, i.e., 0.15 mg/ml and 1.0 mg/ml.**

Given the regulatory requirement for combination products to show "no decrease in safety potency and effectiveness" relative to separate components:

2. **Please discuss the adequacy of the data to assess the significance of the various diminished immune responses observed. Are the data sufficient to establish a minimum threshold of response that can be considered as evidence for efficacy?**

3. **Please discuss the available data on clinical significance of diminished anti-PRP responses observed in certain combination vaccines containing Hib conjugates:**

   a. **In infants and children in the "general" U.S. population**

   b. **In infants and children in clear high-risk populations (e.g., Alaska natives, Native Americans)**

4. **Please discuss whether additional clinical data would be useful in assessing the clinical significance of diminished anti-PRP responses in combination vaccines containing Hib conjugates. Specifically, please discuss the utility of**

   a. **Demonstration of "priming"**

   b. **Demonstration of comparable functional antibody responses, e.g., avidity, isotype, opsonophagocytic antibodies, etc.**

   c. **Comparisons with historical experience and other Hib conjugate vaccines**

   d. **Use of post-marketing data, e.g., controlled studies, epidemiologic surveillance systems, etc.**

Table 1

Anti-PRP responses observed with Combination Products

Combination Vaccine	Point estimate of difference in % responders $\geq$1.0 μg/ml[1]	Confidence interval for the difference[2]
DTaP/PRP-T[a] - study 1: (468-01)	-14.7	-22 to –7
DTaP/PRP-T[b] - study 2 (468-08)	-3.4	-16 to +9
DTaP/PRP-T[c] - study 3 (Rennels)	-29	-40 to –18
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Legend for Table 1 and Figure 1

1 The point estimate for the difference is generated from a comparison of the percentage of children achieving ≥1.0 µg/ml in the group receiving the combination group to that observed in the separate injections control group (C-S) for each study.

2 Confidence interval on the point estimate for the difference in percentage of children achieving ≥1.0 µg/ml when available. NA= not available.

a Study 1 evaluated DTaP vaccine used to reconstitute PRP-T (TriHIBit®, Adventis Pasteur) administered concomitantly with OPV compared to a separate injections control group which received DTaP, PRP-T and OPV concomitantly, but at separate sites. The data represent the difference in the percentage of children achieving an anti-PRP concentration of ≥1.0 µg/ml (with 95% CI) following three doses of vaccine administered at 2, 4, and 6 months of age.

b Study 2 evaluated DTaP vaccine used to reconstitute PRP-T (TriHIBit®, Adventis Pasteur) administered concomitantly with OPV compared to a separate injections control group which received DTaP, PRP-T and OPV concomitantly, but at separate sites. The data represent the difference in the percentage of children achieving an anti-PRP concentration of ≥1.0 µg/ml (with 95% CI) following three doses of vaccine administered at 2, 4, and 6 months of age.

c Study 3 evaluated DTaP vaccine used to reconstitute PRP-T (TriHIBit®, Adventis Pasteur) administered concomitantly with IPV compared to a separate injections control group which received DTaP, PRP-T and OPV concomitantly, but at separate sites. The data represent the difference in the percentage of children achieving an anti-PRP concentration of ≥1.0 µg/ml (with 95% CI) following three doses of vaccine administered at 2, 4, and 6 months of age.

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Table 2
Site-specific differences in Seroconversion when TriHIBit is administered concurrently with IPV[1]

Site	Percent Responders ≥0.15 μg/ml (%)	Percent Responders ≥1.0 μg/ml (%)
Chicago	100	81
New Orleans	90	62

[1]Anti-PRP responses were evaluated at two clinical sites and the percentage of children achieving ≥0.15 μg/ml and ≥1.0 μg/ml anti-PRP concentrations evaluated. The point estimate for the percent responders is noted. Confidence intervals for the point estimate are not available at this time.